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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NASHED, NASHAAT T	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 10/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/825,212	BENSON, TIMOTHY E.	
	Examiner	Art Unit	
	Nashaat T. Nashed, Ph. D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 July 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-53* is/are pending in the application.

4a) Of the above claim(s) *8-46* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 47-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/1/02 & 2/25/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's election with traverse of Group I, claims 1-7 and 47-53, in the reply filed on July 15, 2004 is acknowledged. The traversal is on the ground(s) that one search would produce all he art required for searching all the groups together. This is not found persuasive. The elected invention of Group I is classified in class 435, subclass 189, whereas the inventions of Groups II-VII are classified in different classes and subclasses not required for searching the invention of Group I.

The requirement is still deemed proper and is therefore made **FINAL**.

The use of the trademarks HAMPTON CRYSTAL SCREEN I & II, and WIZARD SCREEN I & II have been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

New corrected drawings in compliance with 37 CFR 1.121(d) are required in this application because Figures 6a-6d are incomprehensible and do not show what is intended to be shown. Applicant is advised to employ the services of a competent patent draftsperson outside the Office, as the U.S. Patent and Trademark Office no longer prepares new drawings. The corrected drawings are required in reply to the Office action to avoid abandonment of the application. The requirement for corrected drawings will not be held in abeyance.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because the specification contains reference to specific amino acid residues not identified by a sequence identification number and the *S. aureus* is not identified by a sequence identification number at each mentioning of the protein. Applicant is required to perfect their compliance with the sequence rules.

Claims 52 and 53 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 52 and 53 are dependent on claim 48, which is directed to a crystal of wild-type *S. aureus* thioredoxin reductase. The dependent claims expand the scope of the parent claims to include fusion protein comprising the amino acid sequence of the *S. aureus* thioredoxin reductase fused to 6 histidine residues at the C-terminus.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following are the reasons for the rejections:

(a) Claims 1 and 4 are narrative in nature and indefinite. It is not clear the nature of the entity being claimed (see (b) and (c) below). Also, it is not clear whether "the wherein" clause modifies thioredoxin reductase-like FAD binding site only, or both thioredoxin reductase and reductase-like FAD binding site. For examination purposes only, the clause is taken to modify only thioredoxin reductase-like FAD binding site because it lacks antecedent bases in thioredoxin reductase.

(b) The phrase "A molecule or a molecular complex" in claims 1, 4, and 7 renders the claims indefinite because the resulting claims do not clearly set forth the metes and bounds of the patent protection desired. It is not clear if the claim is directed to a composition comprising a molecule or molecular complex, or an isolated single molecule, or a model of the active site of a molecule or a molecular complex. For examination purposes, all three meaning of the phrase are assumed.

(c) The phrase "at least a portion of an *S. aureus thioredoxin* reductase" in claim 1, and renders the claim indefinite because the resulting claims do not clearly set forth the metes and bounds of the patent protection desired. For examination purposes only, the phrase interpreted as "at least one atom". It should be noted that atomic coordinated are only meaning full only if they relate spatial relationships of a group of atoms.

(d) The "a set of points" in claims 1 and 4 and renders the claim indefinite because the resulting claims do not clearly set forth the metes and bounds of the patent protection desired. The phrase used in the context of the claim is repugnant to one of ordinary skill in the art because a molecule or molecular structure building block are atoms and not points. The atomic coordinates in table 1 define relative position of atoms and not points.

(e) The phrase "reductase-like FAD binding site" in claims 1 and 4 renders the claims indefinite because the claims include elements not actually disclosed (those encompassed by "reductase-like"), thereby rendering the scope of the claims unascertainable. See MPEP § 2173.05(d).

(f) Tables 1-7 in claims 1-7 contain amino acid residues, presumably, from an amino acid sequence not identified by a sequence identification number, which renders the claims indefinite and confusing. For examination purposes only, the amino acid sequence is assumed to be that of SEQ ID NO: 1. If the examiner assumption is correct, claims 6 and 7 are particularly confusing because residues 164 in Tables 6 and 7 is indicated as leucine residue, whereas residue 164 of SEQ ID NO: 1 is threonine.

(g) The phrase "structurally homologous" in claim 7 renders the claim indefinite because the claim includes elements not actually disclosed (those encompassed by "reductase-like"), thereby rendering the scope of the claims unascertainable. See MPEP § 2173.05(d).

(h) The phrase "at least a portion of the structure coordinates listed in Table 1" in claim 7 renders the claim indefinite because the resulting claims do not clearly set forth the metes and bounds of the patent protection desired. For examination purposes only, the phrase interpreted as "at least one atom". It should be noted that atomic coordinated are only meaning full only if they relate spatial relationships of a group of atoms.

35 U.S.C. 101 reads as follows:
Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1-7 are rejected under 35 U.S.C. § 101 because the claimed invention is directed toward non-statutory subject matter.

If the phrase "A molecule or a molecular complex" is assumed to mean "a *S. aureus* thioredoxin reductase or complex thereof", the following explanation for the rejection applies:

In the absence of the hand of man, naturally occurring proteins and/or nucleic acids are considered non-statutory subject matter. *Diamond v. Chakrabarty*, 206 USPQ 193 (1980). This rejection may be overcome by amending the claims to contain wording such as "An isolated and purified protein or nucleic acid".

If the claim is directed to an active site model as defined partially or fully by the atomic coordinates of Table 1, the following explanation for the rejection applies:

Claims 1-7, directed to a data array describing the active site or the structure of *S. aureus* thioredoxin reductase, claims a compilation or mere arrangement of data. The structure of a protein and its active site are intrinsic properties of the protein. Thus,

the 3-D coordinates of a protein constitute nonfunctional descriptive material without physical structure, and therefore are abstract ideas that are not patent eligible subject matter under 35 U. S. C. 101. See, e.g., *In re* Warmerdam, 33 F.3d 1354-1361, 31 USPQ2d 1754, 1760 (Fed. Cir. 1994).

> The following is a quotation of the first paragraph of 35 U.S.C. 112:
> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7 and 47-53 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 7 is directed to all possible molecule or molecular complexes that are structurally homologous to *S. aureus* thioredoxin reductase. The specification, however, only provides a single representative species from *S. aureus* by these claims. There is no disclosure of any particular structure to function/activity relationship in the single disclosed species. The specification also fails to describe additional representative species of these molecules or molecular complexes by any identifying structural characteristics or properties other than the structure feature recited in claim 7, for which no predictability of activity is apparent. Given this lack of additional representative species as encompassed by the claims, Applicant has failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Claims 47-53 are directed to all possible crystals of *S. aureus* thioredoxin reductase. SEQ ID NO: 1 is fusion protein comprising the polypeptide of *S. aureus* thioredoxin reductase fused to the 6 histadine residues at the C-terminus. The 6-histadine residues are expected to be protonated above pH 7 and impact the isoelectric point of the protein substantially, and hence, its solubility at various pH's. The specification, however, fails to describe sufficient detailed to make the polypeptide of SEQ ID NO: 1, and provide sufficient details to even crystallize the polypeptide of SEQ ID NO: 1. Although example 1 of the specification describes a recombinant method to obtain the polypeptide of SEQ ID NO: 1, the specification fails to provide a public source or cite a reference in which the nucleic acid encoding SEQ ID NO: 1 is disclosed. GH Choi of Human Genome Sciences is assumed not to be a public source for the nucleic acid. Also, the specification fails to describe sufficient details to obtain the crystal of the polypeptide of SEQ ID NO: 1, which is described as an orthorhombic crystal in the space group $P4_32_12$, a = 70 Å, b = 70 Å, and c = 160 Å, $\alpha = \beta = \gamma = 90^{\circ}$. Applicant relies

on a crystallization conditions found in well number 33 of a commercially available kit that comprises 4 M sodium formate to support the disclosure of his crystallization conditions. As indicated above, while the use of trade name is permissible in an application, the generic equivalent should be stated. The content of well number 33 of commercially available product is not known to one of ordinary skill in the art and its generic content should be stated in the specification. Thus, the specification failed to provide sufficient details to allow one of ordinary skill in the art to make the polypeptide of SEQ ID NO: 1, and its crystal. In addition, there is no disclosure of any particular relationship between the space group of the crystal and the crystallization conditions which may be found in HAMPTON SCREEN I kit, well number 33. The specification also fails to describe additional representative species of these crystals by any identifying structural characteristics or properties other than the activity recited in claims 47 and 48, for which no predictability of structure is apparent. Similarly, claims 52 and 53 are directed to all possible crystals of *S. aureus* thioredoxin reductase of SEQ ID NO: 1. The specification fails to describe additional representative species of these crystals by any identifying structural characteristics or properties other than the thioredoxin reductase of SEQ ID NO: 1, for which no predictability of a crystal is apparent. Given this lack of additional representative species as encompassed by the claims, Applicant has failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Claims 1-7, and 47-53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The specification does not enable any person skilled in the art to make and use the invention commensurate in scope with these claims. The claims are broader than the enablement provided by the disclosure with regard to: (a) the huge number of all possible molecules or molecular complexes comprising at least a portion of a *S. aureus* thioredoxin reductase or thioredoxin reductase-like binding site or homologus to an *S. aureus* thioredoxin reductase (claims 1-7); (b) method of crystallizing any polypeptide from *S. aureus* havin thioredoxin reductase and derivatives thereof which include any fusion protein comprising said polypeptide (claim 46); and (c) any crystal comprising any polypeptide from *S. aureus* having thioredoxin reductase activity (claims 48-53). Factors to be considered in determining whether undue experimentation is required, are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention are directed to an isolated single molecule or molecular complex comprising at least a portion of an *S. aureus* thioredoxin reductase or a thioredoxin reductase-like FAD binding site, or a model of said molecule or molecular complex (claims 1-7). Claim 46 is directed to a method of crystallizing any polypeptide from *S. aureus* having thioredoxin reductase activity. Said method of obtaining a crystal by preparing a protein solution comprising 1-50 mg/ml protein which can be crystallized from a solution having pH between 6-10, and comprising about 0-40% DMSO and 100 mM to 6 M sodium formate. Finally, claims 48-53 are directed to any crystal of any *S. aureus* thioredoxin reductase and derivatives (claims 48-51); and any crystal of the amino acid sequence of SEQ ID NO: 1. As indicated above, the specification fails to provide guidance to even make and crystallize the polypeptide of SEQ ID NO: 1. While molecular biological techniques and genetic manipulation to make and use the constructs claimed are known in the prior art and the skill of the artisan are well developed, knowledge regarding isolating a single molecule or molecular complex, all polypeptide having a thioredoxin-like FAD binding site and their three dimensional structure, the crystallization conditions of any polypeptide from *S. aureus* having thioredoxin reductase and its homologues and derivatives, and all possible crystallization conditions which would produce any crystal of the polypeptide of SEQ ID NO: 1 is lacking. Thus, searching for a method to isolate a single molecule or molecular complex, a *S. aureus* thioredoxin reductase-like FAD binding site, a model of said molecule or molecular complex or crystallization conditions of a protein solution containing 1-50 mg/ml protein between pH 6-10 in a solution comprising 0-40% DMSO and 100mM-4.0 M sodium formate or any crystal for SEQ ID NO: 1 is well outside the realm of routine experimentation and predictability in the art of success is extremely low. The amount of experimentation to develop a method to isolate molecule or a molecular complex, or portion thereof or a thioredoxin reductase-like FAD binding site; determining the three dimensional structure of said molecule or molecular complex; crystallizing any *S. aureus* thioredoxin reductase and derivatives in the ranges of pH, and protein, DMSO and sodium formate is enormous. Since routine experimentation in the art does not include screening vast numbers of crystallization conditions, identifying a method that would allow the isolation of a single molecule or molecular complex, determine the three dimensional structure of a protein where the expectation of obtaining the desired molecule or molecular complex, structure, or crystal is unpredictable, the Examiner finds that one skilled in the art would require additional guidance, such as information regarding the exact amino acid sequence to make, the crystallization conditions where a suitable crystal for structure determination by the X-ray diffraction method can be obtained, the 3-D structure of thioredoxine reductase-like FAD binding site. Without such guidance, the experimentation left to those skilled in the art is undue.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the

applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-7 are rejected under 35 U.S.C. 102(e) as being anticipated by U. S. P. 6,767,536 ('536, Ahaonowitz *et al.*).

The '536 patent teaches the nucleic and amino acid sequence of thioredoxin reductase from *S. aureus* of SEQ ID NO: 1 and 2. The amino acid sequence of SEQ ID NO: 2 has 95% sequence identity to SEQ ID NO: 1 of the instant application, 308 amino acids are identical, two mismatch, and lacking the C-terminus His-tag. Thus, the polypeptide of SEQ ID NO: 2 is a *S. aureus* thioredoxin reductase molecule, and is expected to have all the intrinsic properties listed in claims 1-7.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 4, and 7 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Waksman *et al.* (IDS reference: J. Mol. Biol. 1994, 236, 800-816).

Waksman *et al.* teach the crystal structure of three forms *Escherichia coli* thioredoxin reductase: (a) the oxidized form of the enzyme, (b) a variant of said reductase in which Cys-136 is mutated to serine, and (c) a complex between the said variant reductase and NADPH, see the abstract, the material and methods section starting on page 802. Also, they teach the FAD binding site, see the paragraph bridging pages 810 and 811, as well as the NADPH binding site, page 812.

The structures described by Waksman *et al.* appear identical to the molecule or molecular structure of the claims. The thioredoxin reductases from *S. aureus* and *E. coli* share significant amino acid sequence homology, as well as three-dimensional structural homology, see for example Figures 11-13 in the specification. Thus, the molecule or molecular complex taught by Waksman *et al.* comprises at least a portion of

S. aureus thioredoxin reductase or thioredoxin reductase-like FAD binding site (claim 1, and 4-7).

The rejections are being made under 35 U.S.C. § 102(b) and 35 U.S.C. § 103 because it is not possible for the Examiner to physically compare the claimed molecule or molecular complex and those reported by Waksman *et al.* Applicant bears the burden of providing evidence, which distinguishes the claimed molecule or molecular complex from those disclosed by Waksman *et al.* A preferred means of providing this evidence is for applicant to submit a side-by-side comparison between the molecule or molecular complex of the prior art and the claimed molecule or molecular complex which demonstrates any material differences and shows the claimed molecule or molecular complexes to be distinct and unobvious in view of the molecule or molecular complexes of the prior art. *In re Best, Bolton, and Shaw* 195 USPQ 430 (CCPA 1977) and *In re Fitzgerald, Sanders and Bagheri* 205 USPQ 594 (CCPA 1980).

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Art Unit 1652